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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,200	01/16/2002	Anne M. Fourie	ORT-1417	6279

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/050,200	FOURIE ET AL.	
	Examiner	**Art Unit**	
	Malgorzata A. Walicka	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): see the attached.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see the attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *7-19 and 21*.

   Claim(s) withdrawn from consideration: _____.

8. ☒ The drawing correction filed on *04 August 2003* is a)☒ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *09/02/03,06/18/02*.

10. ☐ Other: _____

Amendment of Oct. 4, 2004 is acknowledged. The amendments to the claims have been entered. Claims 1-6 were previously canceled; claim 20 has been currently canceled. Claims 7, 9-12, 14, and 16-19 has been currently amended. Claims 7-19 and 21 are pending and subject of this Advisory Action.

1. Rejections

1.1. 35 USC, section 112, second paragraph

Rejection of claims 14-16 under 35 U.S.C. 112 made in the final Office Action is withdrawn, because claim 14 has been amended.

1.2. 35 USC, section 112, first paragraph

1.2.1. Lack of written description

Rejection withdrawal

Rejection of claim 20 is moot because the claims have been cancelled.

Rejection of claims 7-19 and 21 for new matter is withdrawn, because the claims have been amended.

Rejection of claims 7–19 and 21 under 35 U.S.C. 112, first paragraph, because neither the claims nor the specification teach that the inhibitor of the truncated form of aggrecanase inhibits also the full- length enzyme, is withdrawn, because the claims are now limited to truncated forms of the enzyme that have metalloprotease activity.

Rejection maintained

Claims 7-9, 11-13, 17-19 and 21 rejected in the Office Action of Nov 17, 2003 for lack of sufficient written description remain rejected. The claims are directed to a method of use of a large and variable genus of peptides that are less that 40 amino acids in length wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides. Applicants disclose several representatives of the claimed genus identified by SEQ ID NOs: 3, 4, 5, 6 and 7. This is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants fail to disclose any particular structure to function (of being cleavable by the truncated aggrecanase –1 and –2, i.e., SEQ ID NO: 8 and 9 or by any metalloprotease of any aggrecanase) relationship for a polypeptide that is less than 40 amino acids in length, wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side of said polypeptide. No information, beyond the characterization of SEQ ID NO: 3, 4, 5, 6 and 7 has been provided by Applicants, which would indicate that they had possession of the claimed genus of these polypeptides. The data presented in Fig. 2 clearly prove that predictability of the function of the representatives of the claimed genus is not apparent. Some of the peptides are good substrates for metallopreotease derived from aggrecanse –1 and some are good substrates for metalloprotease derived from aggrecanase –2, and claim 17 and dependent claims are limited to any

aggrecanses , not only to aggrecanase-1 and –2. The fact that a polypeptide of less than 40 amino acid long comprises a glutamic acid and as a neighbor on the C – terminal side of said glutamic acid a non-polar or uncharged amino acid is not sufficient for the polypeptide to be cleavable by SEQ ID NO: 8 or 9 or by full length ADAMTS-4 and ADAMTS-11. In addition, it is even less apparent which of such polypeptides are the substrates for metalloprotease from any aggrecanase, its mutated form or aggrecanase from different animal species.

Given the lack of structural characteristics of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed. Thus, the rejection of claims 7-9, 11-13, 17-19 and 21 is not withdrawn.

1.2.2. Scope of invention

Claim 7-19 and 21 remain rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for methods to detect compounds that inhibit aggrecanase-1 and –2 (metalloproteases of SEQ ID NO: 8 and 9) using peptides of SEQ ID NO: 3, 4, 5, 6 and 7 does not reasonably provide enablement for methods to detect compounds that inhibit any metalloprotease or any agrecanase (full-length aggrecanase) using any peptide less than 40 amino acids in length comprising a cleavage site for any truncated aggrecanase wherein said site is located between a

glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass any method of identifying an inhibitor of any wild type aggrecanase using any peptide less than 40 amino acids in length and comprising a cleavage site for any truncated, metalloprotease form of aggrecanase from any natural or man-made source, wherein said cleavage site is between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

Providing any truncated aggrecanase comprising the metalloprotease region of the enzyme and/or full-length aggrecanase covered by the scope of the invention requires cloning extremely large number of genes originating from any animal or gene bank. The genes should be subsequently expressed in their full length or any truncated form comprising a metalloprotease, and encoded polypeptide tested for metalloprotease

activity using a standard substrate, i.e. agreccan fragment of more than 40 amino acids comprising as the cleavage site Glu-Ala mimicking residues Glu373-Ala374 of aggrecan molecule. After being successful in these lengthy and tedious procedures that are out of realm of the routine experimentation in the art, one skilled in the art has to design the polypeptides with the desired characteristics and test them for being a substrate for any of truncated aggrecanase chaving metalloprotease activity.

While providing a peptide with claimed characteristics as a candidate substrate for aggrecanase truncated to metalloprotease, has certain probability of success, Applicants' own investigations indicate that this probability is low, therefore undue experimentationis necessary.

Traversing this rejection Applicants write in Remarks to the final rejection (the paragraph bridging page 78 and 9,

"the attributes and features of all species within the claimed genus include: (i) amino acid sequence; (ii) less than 40 amino acid in length; (iii) containing a cleavage site between a glutamic acid an N-terminal side of the cleavage site and a non-polar or unchareged amino acid residue on a C-terminal side of the cleavage site; and (iv) are capable of being cleaved by the inventive metalloprotease enzyme's of invention."

Applicant's arguments have been fully considered but are found not persuasive for the following reasons. Applicants' data presented in Figure 2 provide an evidence that in case of aggrecanase-1 the probability that the polypeptide having the indicated

characteristics is a substrate is about 10% (6/56, taking those polypeptides for which the activity of cleaving is about 0.1 units) and in the case of aggrecanase-2 is even less, about 7% (4/56, taking into account those peptides for which the activity of cleaving is about 0.5 units). The probability of finding a peptide with the described characteristics that is a substrate for any truncated aggrecanase having metalloprotease activity is even less, because Applicants' own data from Fig. 2 indicate that the probability of finding peptide that is a substrate for both SEQ ID NO: 8 and 9 is about 3/56, i.e., about 6%; see also page 5, line 31 of the specification where Applicants state, "One peptide [out of 56 tested, MW] was a good substrate for both truncated aggrecanase –1 and truncated aggrecanase –2." The one peptide out of 56 is less than 2%. More important, Applicants teach that the one out of 56 polypeptides is a substrate for metalloproteases derived from ADAMTS-4 and ADAMTS5/11 but the specification does not teach it is a substrate for any other metalloprotease from any aggrecanase.

In summary, rejection of claims 7-19 and 21 under scope of enablement is not withdrawn.

2. Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

REBECCA E. PROUTY
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